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Method

The present invention relates to a method for the production of hyperpolarized ^{129}Xenon and to a method for the production of a contrast agent.

^{129}Xenon is a gas at room temperature. The nucleus has a spin quantum number of ½, and a moderately large nuclear magnetic moment of -1.347494 nuclear magnetons. It can be taken up into the lungs and absorbed into blood or tissue. It has been recognized that it has potential to be imaged in the body via magnetic resonance imaging (MRI). However, since the gas phase is approximately 1000 times less dense (in moles/liter) than the condensed phase of biological material (e.g. blood, tissue), its nuclear magnetic resonance (NMR) signal is much weaker than that of the protons in the condensed biological material. To surmount this, hyperpolarized ^{129}Xenon has been prepared. In this case, the nuclear magnetization, upon which the MRI sensitivity depends, can be increased by 5 orders of magnitude, making the contrast available with the ^{129}Xenon even in the gas phase larger than that from the protons in their equilibrium room temperature condensed phases. Because the spin is ½, the retention time of the non-equilibrium highly polarized state of the hyperpolarized ^{129}Xenon, frequently referred to as the spin-lattice relaxation time T_1, is long enough even at body temperature for the ^{129}Xenon to persist in the hyperpolarized state for sufficient time to obtain contrast enhanced MR images. Thus, hyperpolarized ^{129}Xenon gas has generated considerable interest as an inhalable contrast agent for magnetic resonance imaging of the lungs.

W. Happer et al., Phys. Rev. A29, 3092 (1984) described the production of hyperpolarized ^{129}Xenon using optical pumping laser techniques. A disadvantage of this method is the low production rate, due to polarization being achieved in the low density gaseous phase. Thus, only rates of a few liters per hour are achievable.

WO-A-99/35508 discloses hyperpolarization of Xenon in the solid state using the "brute force" method or the dynamic nuclear polarization (DNP) method.

WO-A-00/23797 discloses additional methods for the hyperpolarization of Xenon in the solid state, such as doping xenon with paramagnetic oxygen molecules,

irradiating the xenon with ionizing radiation or the dispersal of magnetized small particles encapsulated in polymers which are placed in the xenon.

It has now surprisingly been found that the presence of an additive in DNP hyperpolarization of Xenon in the solid state dramatically increases polarization enhancement.

The present invention provides a method for producing hyperpolarized ^{129}Xenon comprising

a) preparing a mixture of Xenon, an additive and a free radical

b) hyperpolarizing said mixture according to the DNP method to obtain hyperpolarized ^{129}Xenon and

c) optionally separating said Xenon from the other components of the mixture.

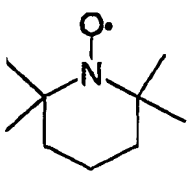
In a first step a) a mixture of Xenon, an additive and a free radical is prepared.

According to the invention, Xenon can be used in its natural form, i.e. a mixture of several isotopes including ^{131}Xenon (21.2%) and ^{129}Xenon (26.4%). Alternatively, ^{129}Xenon enriched Xenon can be used.

The term "additive" according to the invention encompasses also suitable mixtures of additives. Preferably, solvents are used as additives in the method according to the invention. More preferably, additives are lipophilic solvents and/or solvents which contain a high amount of NMR active nuclei such as ^{1}H, ^{19}F, ^{31}P and the like. Particularly preferably, the additive is a solvent selected from the group consisting of straight chain or branched C_6-C_{12}-alkanes, C_5-C_{12}-cycloalkanes, fatty alcohols, fatty esters, substituted benzene derivatives like toluol or xylene and mono- or polyfluorinated solvents like tetradecafluorohexane or hexafluoroisopropanol. Most preferred additives are cyclopentane, toluene or xylene.

The free radical in the mixture of step a) may either be a stable free radical such as a nitroxide or a trityl radical or a free radical prepared *in situ* from a stable radical precursor by a radical-generating step shortly before the hyperpolarization step b), or alternatively by the use of ionising radiation. Suitable free radicals are organic free

radicals such as triarylmethyl, nitroxide radicals such as porphyrexide, TEMPO, TEMPONE and TEMPOL (see below), oxygen centered radicals such as galvinoxyl (see below), carbon centered radicals such as trityls and allyls, metal ions with unpaired electrons such as Cr(V), e.g. BHHA-Cr(V) and EHBA-Cr(V) (see below), Mn(II), e.g. $MnCl_2$, Tm(II), Yb(III), Nd(III), V(IV), Ni(II) and Fe(III) ions or radiation generated radical centers and biradicals, e.g. those described in WO-A-88/10419, WO-A-90/00904, WO-A-91/12024, WO-A-93/02711 and WO-A-96/39367. Preferred free radicals are those which dissolve in the additive and/or in liquid Xenon. Particularly preferred free radicals are trityls and nitroxide radicals, e.g. tert.-amyl-tert.-butyl nitroxide.



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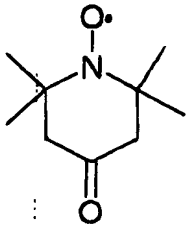

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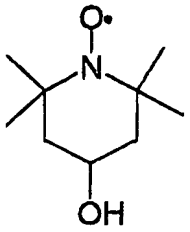

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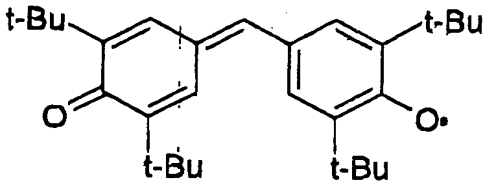
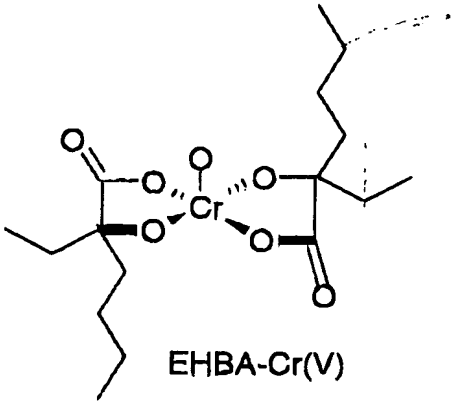
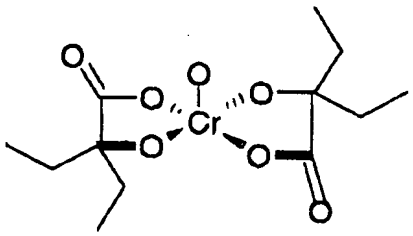


galvinoxyl



EHBA-Cr(V)



BHHA-Cr(V)

In a preferred embodiment, Xenon gas is condensed on top of the additive and free radical in a suitable reaction vessel, preferably by using a liquid nitrogen bath. The reaction vessel is subsequently sealed and warmed up until the components are in the liquid state. The additive and the free radical are mixed with the liquid Xenon until a homogeneous mixture is obtained. The formation of a homogeneous mixture may be achieved by several means known in the art such as agitation, shaking, stirring and the like. The resulting mixture is then cooled rapidly, e.g. in a liquid nitrogen bath, and the solid obtained is used for the hyperpolarization.

In a second step b), the mixture of step a) is hyperpolarized according to the DNP method to obtain hyperpolarized ^{129}Xenon.

Suitably, the mixture will be cooled, e.g. in liquid nitrogen, in order to result a solid which can be used for the DNP hyperpolarization.

DNP mechanisms include the Overhauser effect, the so-called solid effect and the thermal mixing effect. During the DNP process, energy, normally in the form of microwave radiation, is provided. There is a transfer of polarization from the unpaired electron of the radical to ^{129}Xenon and/or the NMR active nuclei of the additive, depending on the properties of the free radical and/or the frequency of the microwave radiation applied. If the NMR active nuclei of the additive are polarized, this polarization may be transferred to ^{129}Xenon subsequently by a suitable cross-polarization sequence. The DNP method may utilize a moderate or high magnetic field and a very low temperature, e.g. by carrying out the DNP process in liquid helium and a magnetic field of about 1 T or above. The temperature should be very low, e.g. 100 K or less, preferably 4.2 K or less, more preferably 1.5 K or less, especially preferably 1 K or less and even more especially preferably 100 mK or less. The magnetic field strength used should be as high as possible, suitably higher than 0.1 T, preferably higher than 1 T, more preferably 5 T or more, especially preferably 15 T and more and most preferably 20 T and more. Alternatively, a moderate magnetic field and any temperature at which sufficient enhancement is achieved may be employed. Preferably, the polarization should 1% or more, more

preferably 10% and more, especially preferably 25% and more and most preferably 50% and more.

After hyperpolarization, Xenon may be separated from the other components of the mixture by simply warming the mixture until Xenon is in a gaseous state and collecting the gas in a suitable container. Optionally, the gas can be condensed again to obtain "Xenon ice" which can be transported using a permanent magnet and a liquid nitrogen bath. Preferably, the magnetic field strength for such a transport should be as high as possible, suitably 10 mT or more, preferably 0.1 T or more, more preferably 0.2 T or more and especially preferably 0.3 T or more. The temperature for such a transport should be below the boiling point of Xenon, i.e. below 166.05 K at atmospheric pressure.

For the use as a contrast agent, the condensed Xenon may conveniently be heated prior to said use.

Thus, another aspect of the invention is a method for the production of a contrast agent comprising

a) preparing a mixture of Xenon, an additive and a free radical
b) hyperpolarizing said mixture according to the DNP method to obtain hyperpolarized ^{129}Xenon
c) separating Xenon from the other components of the mixture, and
d) optionally condensing the separated Xenon again.

Yet another aspect of the invention is the use of DNP-hyperpolarized ^{129}Xenon for the manufacture of a contrast agent for the use in magnetic resonance imaging of the human or non –human animal body, preferably of the lungs of the human or non-human animal body.

Yet another aspect of the invention is a method for magnetic resonance imaging of the lungs of a human or non-human animal body comprising

a) preparing a mixture of Xenon, an additive and a free radical
b) hyperpolarizing said mixture according to the DNP method to obtain hyperpolarized ^{129}Xenon

c) separating said Xenon from the other components of the mixture,

d) optionally condensing and heating said separated Xenon

e) administering said Xenon to the lungs of a human or non-human animal body and

f) generating magnetic resonance images of said body.

Yet another aspect of the invention is the use of ^{129}Xenon which has been hyperpolarized according to the method of the invention as a contrast agent, more preferably as a contrast agent for magnetic resonance imaging of the lungs.

Examples

Example 1 (comparison example)

10 μl of tert.-amyl-tert.-butyl-nitroxide in a reaction vessel were cooled in a liquid nitrogen bath. 750 ml of gaseous Xenon (natural abundance ^{129}Xenon, STP) were condensed into the reaction vessel. The reaction vessel was sealed and the temperature was adjusted to 195 K. The content was agitated until a homogeneous liquid was formed and then cooled down in a liquid nitrogen bath. The reaction vessel and the liquid nitrogen bath were then moved to a N_2-glove box. The reaction vessel was opened and liquid nitrogen was added. The solid content of the reaction vessel was pulverized with a spatula and transferred to a pre-cooled sample holder. The sample was then rapidly inserted into a cryostat and DNP polarization was performed using a magnetic field of 3.35 T, an irradiation frequency of 93.3 GHz and a temperature of 1.6 K.

T_1 was measured to ca. 10 h at 1.6 K and 3.35 T. No DNP effect was observed.

Example 2 (comparison example)

Example 2 was carried out as Example 1 using 100 μl of tert.-amyl-tert.-butyl-nitroxide. T_1 was measured to ca. 1 h at 1.6 K and 3,35 T. No DNP effect was observed.

Example 3

Example 2 was carried out as Example 1 using 10 μl of tert.-amyl-tert.-butyl-nitroxide in 1.2 ml toluene and 800 ml of gaseous ^{129}Xenon. DNP polarization was performed using a magnetic field of 3.35 T, an irradiation frequency of 93.3 GHz and a temperature of 1,44 K. A polarization enhancement of 24 was measured at 1.44 K and 3.35 T, corresponding to a polarization of ^{129}Xenon of 1.6%.

Claims:

1. A method for producing hyperpolarized ^{129}Xenon comprising
   a) preparing a mixture of Xenon, an additive and a free radical
   b) hyperpolarizing said mixture according to the DNP method to obtain hyperpolarized ^{129}Xenon and
   c) optionally separating said Xenon from the other components of the mixture.

2. A method according to claim 1 wherein the additive is a solvent, preferably a lipophilic solvent and/or a solvent which contains a high amount of NMR active nuclei.

3. A method according to claim 1 and 2, wherein the additive is a solvent or a mixture of solvents selected from the group consisting of straight chain or branched C_6-C_{12}-alkanes, C_5-C_{12}-cycloalkanes, fatty alcohols, fatty esters, substituted benzene derivatives like toluol or xylene and mono- or polyfluorinated solvents like tetradecafluorohexane or hexafluoroisopropanol.

4. A method according to claims 1 to 3 wherein the mixture in step a) is prepared from liquid Xenon.

5. A method according to claims 1 to 4 wherein the mixture in step a) is prepared by condensing Xenon gas on the top of the additive and the free radical, warming the components until Xenon and the additive are in a liquid state and mixing the components until a homogeneous mixture is obtained.

6. A method according to claims 1 to 5 wherein in step b) ^{129}Xenon is directly hyperpolarized.

7. A method according to claims 1 to 6 wherein in step b) the NMR active nuclei of the additive are hyperpolarized and this polarization is subsequently transferred to ^{129}Xenon by a cross-polarization sequence.

8. A method according to claims 1 to 7 wherein Xenon enriched with ^{129}Xenon is used.

9. A method according to claims 1 to 8 wherein in step c) Xenon is separated from the other components of the mixture by warming the mixture until Xenon is in the gas state and collecting said Xenon in a suitable container.

10. A method for the production of a contrast agent comprising

a) preparing a mixture of Xenon, an additive and a free radical

b) hyperpolarizing said mixture according to the DNP method to obtain hyperpolarized ^{129}Xenon

c) separating said Xenon from the other components of the mixture, and

d) optionally condensing the separated Xenon again.

12. Use of DNP - hyperpolarized ^{129}Xenon for the manufacture of a contrast agent for the use in magnetic resonance imaging of the human or non –human animal body, preferably of the lungs of the human or non-human animal body.

Abstract

The present invention relates to a method for the production of hyperpolarized ^{129}Xenon and to a method for the production of a contrast agent.